REMARKS

Reexamination and reconsideration is respectfully requested in light of the foregoing amendments and following remarks.

Claims 1-30 are pending in this application. Claims 13-18 and 28-30 have been withdrawn from consideration due to a restriction requirement. Applicant notes the Examiner's treatment of the election as being a election made without traverse. Claims 1, 2, 7 and 19 have been amended. No new matter has been added to the application by these amendments. Claim 7 has been amended to delete subject matter while independent claims 1, 2 and 19 have been amended to change "a nucleotide" at the end of step (a) to be "at least dATP or ddATP." Support for the amendments can be found at page 4, lines 18-24; page 26, line 10; page 49, lines 12 and 13; and page 56, line 26 of the specification.

Applicant notes the Examiner's consideration of the information cited in the Information Disclosure Statement filed October 1, 2003, as acknowledged in the Office Action Summary. Applicant further notes the Examiner's acknowledgment of Applicants' claim for foreign priority under 35 U.S.C. § 119.

Objections to the Specification

Applicant notes the Examiner's advisory regarding foreign priority under 35 U.S.C. § 119(a)-(d). While Applicant does not find any basis in the record for provoking an interference, a translation of the foreign priority document is attached to this response as required by the Examiner. With this submission, it is respectfully requested that this objection be reconsidered and withdrawn.

The Examiner notes that Applicants have filed to comply with 37 C.F.R. § 1.821 - 1.825. As a result of telephone conferences with the Examiner on November 10, 2005, December 20, 2005 and December 21, 2005, Examiner clarified her position in the Office Action and indicated that drawing Figs. 14, 16 and 18 needed to be corrected to include the sequence id numbers in the drawing figures. Accordingly, Figs. 14, 16 and 18 of the drawings have been corrected to include the sequence id numbers. Replacement sheets for drawing Figs. 14, 16 and 18 are attached to this response. The sequence id numbers have been inserted above each sequence listing. Also, a marked-up version of the drawings changes are attached with the drawing changes marked in red. It is respectfully requested that the replacement sheets for drawing Figs. 14, 16 and 18 be approved and enter by the Examiner.

The Examiner objects to the use of embedded hyperlink or browser-executable codes. The Examiner notes the hyperlink code in the paragraph at page 6, lines 14-17. The paragraph has been amended to delete the hyperlink code. By this amendment, the objection should be overcome.

The Examiner objects to the title of the invention as being too long. The title has been amended to shorten the title to: METHOD FOR DETECTING EXTENSION REACTION WITH PRIMERS. By this amendment, the objection should be overcome. It is respectfully requested that this objection be reconsidered and withdrawn.

Objection to the Abstract

The Examiner objects to the Abstract as being too long, i.e., more than 150 words. The Abstract has been amended to less than 150 words. A clean copy of the Abstract is attached to this response.

Informalities

The Examiner finds that the use of "the step" in each step of claims 1, 2 and 19 is redundant since the preamble of each claim recites that the method comprises steps. Claims 1, 2 and 19 have been amended to revise each step of the claimed method to delete the phrase "the step". It is believed that by these amendments to the claims the informality is overcome.

Rejection for Obviousness

Claims 1-12 and 19-27 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Nyren et al. (WO 98/13523) and Zhen et al. [*J. Biol. Chem.*, Vol. 272(35), pp 22340-348 (1997)]. According to the Examiner, Nyren et al. teach (i) detecting and extension reaction, (ii) identifying or detecting a base at a target nucleic acid sequence, (iii) detecting extension products and identifying a single base polymorphism and base sequence of the target nucleic acid, (iv) using two different nucleotides to discriminate a base type; (v) PPi release is measured electrically, and (vi) the extension reaction is performed using polymerase chain reaction (PCR). The Examiner recognizes that Nyren et al. fails to teach "contacting sample solution with a permeable membrane having H^+ pyrophosphatase which hydrolyses pyrophosphate released during extension reaction and measuring the H^+ concentration either in solution on the front face of the membrane or in the solution at the back face of the membrane" or using a pH sensitive pigment, acridine orange. For this deficiency, the Examiner relies on the teachings of Zhen et al. The Examiner concludes that the combined teachings of Nyren et al. and Zhen et al. would have rendered the invention obvious.

Independent claims 1, 2 and 19 have been amended to change "a nucleotide" at the end of step (a) to be "at least dATP or ddATP." Support for the amendments can be found at page 4,

lines 18-24; page 26, line 10; page 49, lines 12 and 13; and page 56, line 26 of the specification. The prior art cited by the Examiner teaches away from using dATP or ddATP for the nucleotide.

Nyren et al. discloses measuring that the concentration of pyrophosphoric acid (PPi) released from the polymerase reaction using luciferase. The reaction mechanism is a two step process which involves using an analog of ATP, and not dATP or ddATP, for the nucleotide. Specifically, in the first reaction, APS (adenosine 5'-phosphosulfate) reacts with PPi in the presence of ATP sulfurylase to generate ATP and a sulfate ion. The ATP reacts with the enzyme luciferine in the presence of oxygen and light (hv) is emitted indicating the presence of PPi. The reaction schemes are set forth below:

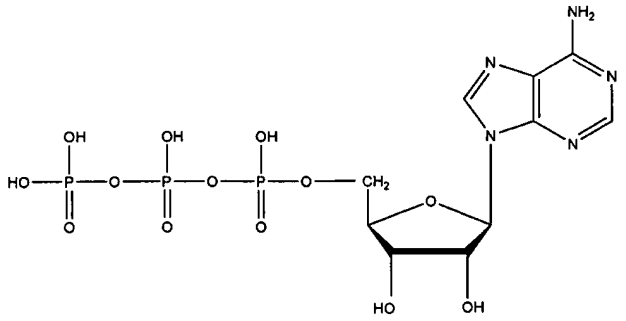
$$PPi + APS \xrightarrow{\text{(ATP sulphurylase)}} ATP + SO_4^{=}$$

$$ATP + \text{luciferin} + O_2 \rightarrow \text{oxylucifcrin} + AMP + PPi + CO_2 + H_2O + hv$$

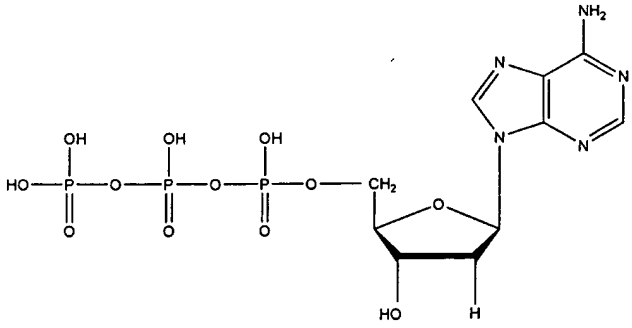
The reaction scheme disclosed by Nyren et al. would not have led a person having ordinary skill in the art to the claimed invention. First, the reaction scheme requires the use of a total of five reagents and enzymes. The present invention requires a nucleic acid, a primer and either dATP or ddATP. Second, in the extending reaction of the primer, an analog of dATP or ddATP must be used instead of dATP or ddATP because dATP or ddATP interferes with the luciferase reaction (Nyren: page 3, lines 12-18 and page 3, line 26 to page 4, line 11). Third, the reaction scheme of the present invention does not involve using the luciferase enzyme.

For reasons set forth below, there is no motivation to modify Nyren et al. by the teachings of Zhen et al. to use a H+ permeable membrane having H^+-pyrophosphatase. The formulas below show the chemical structures of ATP, dATP and ddATP, respectively:

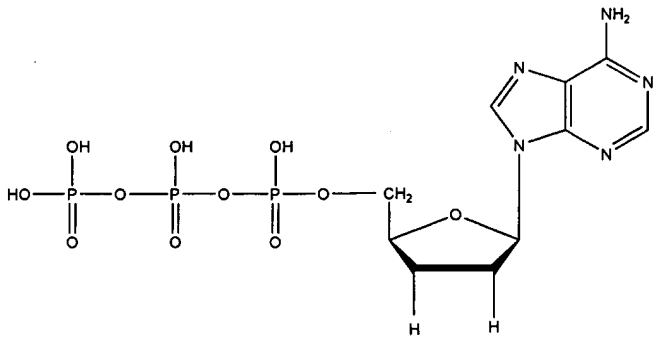
ATP



dATP



ddATP



The chemical structures of ATP, dATP and ddATP are similar. They differ with respect to the hydroxyl groups coupled to the carbon atom at positions 2 and 3 of the furanose ring. It would have been expected that dATP or ddATP would react in a similar manner as ATP in the second step of Nyren's reaction scheme. In enzymatic reaction of the present invention, H^+-pyrophosphatase is used for detecting PPi. Therefore, dATP or ddATP will not interfere with the reaction of detecting PPi. Therefore, in the present invention, unlike Nyren et al, dATP or ddATP can be used as the nucleotide in extending reaction.

Zhen et al. do not make up for the deficiencies of Nyren et al. Zhen et al. disclose detecting H^+ transferred by H^+-pyrophosphatase, but the patent does not disclose or suggest anything about primer extending reaction and the problems caused by using dATP or ddATP for supplying adenine as one of bases in the primer extending reaction combined with the reaction using luciferase. Moreover, the Examiner has not presented any cogent scientific reasoning to support her conclusion of that a person having ordinary skill in the art would have been motivated from the teachings of Zhen et al. to modify Nyren et al. to include the membrane for detecting and measuring H^+ transferred by H^+-pyrophosphatase.

Any suggestion for substituting the H^+ permeable membrane in place of Nyren's means for measuring PPi could only have come from Applicant's disclosure. Combining the references as suggested by the Examiner would destroy the invention disclosed by Nyren et al. Nyren et al teaches away from using dATP and ddATP. The Examiner's reasoning that there would have been motivation to modify Nyren et al. because "Zhen et al. explicity taught the use of membrane associated H^+ pyrophosphatase in measuring the differences in PPi hydrolysis and H^+ translocation of mutant and wild type ... and [that] such modification of the method would be

[sic, have been] obvious over the cited prior art in the absence of secondary considerations" is conclusionary at best, and does not explain how Nyren's reaction scheme would have been modified to arrive at the claimed invention and what teaching in the Zhen et al. reference would have led a person having ordinary skill in the art to modify Nyren's reaction scheme to accommodate Zhen's membrane associated H^+ pyrophosphatase.

For all of the foregoing reasons, it is respectfully submitted that the combined teachings of Nyren et al. and Zhen et al. would not have led a person having ordinary skill in the art to the invention recited in claims 1-12 and 19-27. Accordingly, it is respectfully requested that the rejection under 35 U.S.C. 103(a) be reconsidered and withdrawn.

Double Patenting Rejection

Claims 1-12 and 19-27 are provisionally rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over claims 1, 3-9 and 14-19 of copending application No. 10/727,664 (U.S. Publication No. 2004/0197803). A Terminal Disclaimer is attached to this response. It is respectfully requested that the terminal disclaimer be approved and entered to overcome the obviousness-type double patenting rejection.

Conclusion

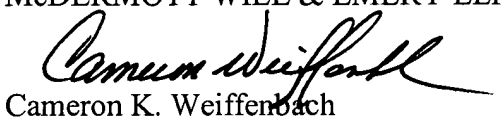
For the foregoing reasons, it is submitted that the claims 1-12 and 19-27 are patentable over the teachings of the prior art relied upon by the Examiner. Accordingly, favorable reconsideration of the claims is requested in light of the preceding amendments and remarks. Allowance of the claims is courteously solicited.

If there are any outstanding issues that might be resolved by an interview or an Examiner's amendment, the Examiner is requested to call Applicants' attorney at the telephone number shown below.

To the extent necessary, a petition for an extension of time under 37 C.F.R. § 1.136 is hereby made. Please charge any shortage in fees due under 37 C.F.R. § 1.17 and due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

McDERMOTT WILL & EMERY LLP



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Date: December 22, 2005

Please recognize our Customer No. 20277 as our correspondence address.

(a) Primer C (SEQ ID NO: 1)

5' GATGAGTTCGTGTCCGTACAACTGG 3'

Primer D (SEQ ID NO: 2)

5' GAATCACGGTATCCGGCTGCGCTGA 3'

(b)

	PCR reaction liquid G	PCR reaction liquid H
TaKaRa La Taq	0.2μL	0.2μL
2×GC buffer I	10μL	10μL
dNTP mixture	3.2μL	3.2μL
Sample liquid A or B	4μL (Sample liquid A)	4μL (Sample liquid B)
Primer solution E	0.9μL	0.9μL
Primer solution F	0.9μL	0.9μL
Distilled water	0.8μL	0.8μL

(c)

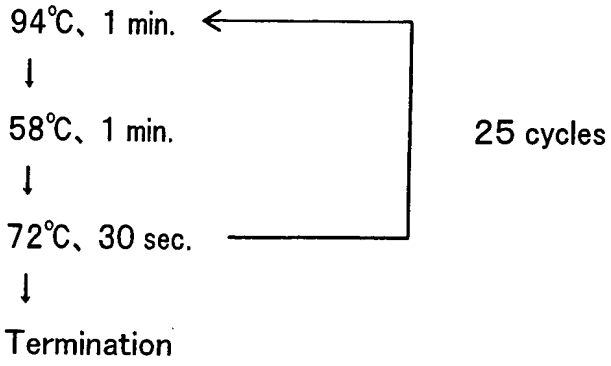

Fig. 14

(a)

- Wild type λ DNA (SEQ ID NO: 3)

5' GATGAGTTCGTGTCCGTACAACTG 3'

3' CTACTCAAGCACAGGCATGTTGAC 5'

R_1

- Mutant λ DNA (SEQ ID NO: 4)

5' GATGAGTTCGTGTCCGTACAACTA 3'

3' CTACTCAAGCACAGGCATGTTGAT 5'

R_2

- Typing primer (SEQ ID NO: 5)

5' GATGAGTTCGTGTCCGTACAACTG 3'

(b)

	PCR reaction liquid I	PCR reaction liquid J
TaKaRa Taq	0.1 μL	0.1 μL
10×PCR buffer	2 μL	2 μL
dNTP mixture	1.6 μL	1.6 μL
Wild type λ DNA liquid or Mutant λ DNA liquid	2 μL (Wild type λ DNA liquid)	2 μL (Mutant λ DNA liquid)
Typing primer solution	0.9 μL	0.9 μL
Primer solution F	0.9 μL	0.9 μL
Distilled water	12.5 μL	12.5 μL

(c)

94℃, 1 min.

↓

58℃, 1 min.

↓

72℃, 20 sec.

↓

Termination

15 cycles

Fig. 16

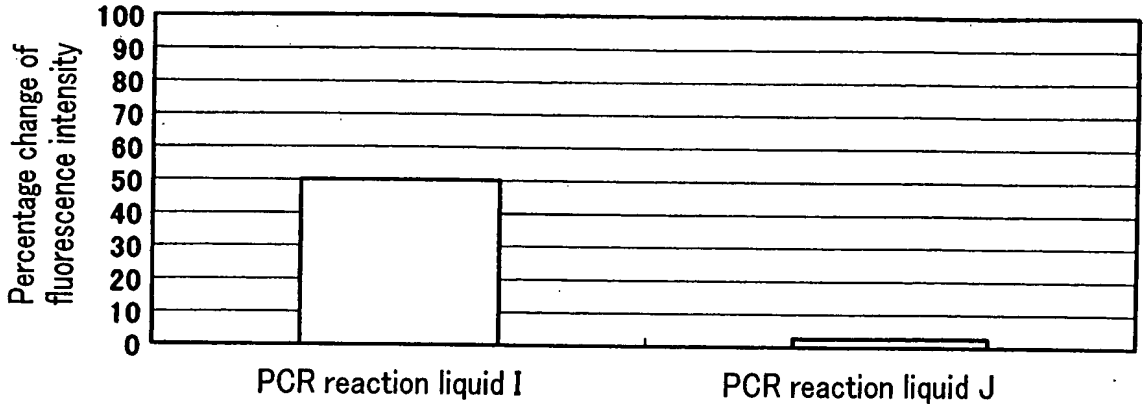

Fig. 17

(a)

・Primer 3 (SEQ ID NO: 6)

5' GATGAGTTCGTGTCCGTACAACT 3'

(b)

	Extension reaction liquid K	Extension reaction liquid L
TaKaRa Taq	0.1μL	0.1μL
10×PCR buffer	2μL	2μL
dATP solution	1.6μL	1.6μL
Wild type λ DNA liquid or Mutant λ DNA liquid	8μL (Wild type λ DNA liquid)	8μL (Mutant λ DNA liquid)
Primer solution M	0.9μL	0.9μL
Distilled water	12.5μL	12.5μL

(c)

94℃、1 min.

↓

58℃、1 min.

↓

72℃、20 sec.

↓

Termination

30 cycles

Fig. 18